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C-2 FUNCTIONALIZED N^6-CYCLOSUBSTITUTED ADENOSINES: HIGHLY SELECTIVE AGONISTS FOR THE ADENOSINE A_1 RECEPTOR

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Abstract: Synthesis of novel N^6-cyclosubstituted isoguanosines and related C-2 functionalized compounds utilizing methodologies with key thermal radical and photochemical steps developed in our laboratory is described. Data on the affinities of these new compounds for the adenosine A_1 and A_2 receptors clearly show that a number of N^6-cyclosubstituted isoguanosines show excellent A_1 agonist activity with the best activity and selectivity being associated with five-membered ring mono- or bicyclic systems at the N^6-position Interestingly, 2-iodo-N^6-cyclopentyladenosine also shows excellent A_1 receptor binding and A_2/A_1 selectivity.

Introduction

In 1929, Drury and Szent-Gyorgyi discovered that the natural ribonucleoside, adenosine, exhibited profound cardiovascular effects.[1] The biochemical basis for the physiological effects of adenosine has been the subject of numerous investigations since that time.[2] These studies have revealed that purinergic receptors termed P_1 (sensitive to adenosine) and P_2 (sensitive to ATP) are apparently involved.[3] Further studies of the effect of adenosine and its metabolically stable analogs on cyclic AMP formation led to the identification of two different extracellular subtypes of the P_1 receptor referred to as A_1 and A_2[4,5] which are apparently found in a wide variety of cells in the human system The A_1 receptor is associated with a decrease in adenylate cyclase activity and the A_2 receptor with an increase in adenylate cyclase activity There is apparently a third subtype of the P_1 receptor which is intracellularly located on the catalytic subunit of adenylate cyclase.[4]

The cardiovascular system has continued to be a main area of interest with regards to possible therapeutic applications of adenosine and its analogs Adenosine itself is not especially useful as a blood pressure reducing agent due to its fast uptake into cells and its rapid metabolic inactivation in the bloodstream[6] However, the natural minor nucleoside, isoguanosine (2-hydroxyadenosine) has been reported to have hypotensive properties greater than adenosine and to be metabolically resistant to deamination by adenosine deaminase[7,8] The central nervous system effects of adenosine have also received much attention Adenosine has been referred to as a neuroprotective compound Brain levels of adenosine massively increase following metabolic insults such as ischemia, hypoxia, hypercapnia, hypoglycemia, and seizures.[9] Anticonvulsant effects of adenosine are believed to be mediated *via* A_1-type receptors[10]

There has been considerable interest in developing adenosine receptor agonists that have better pharmacological properties than adenosine both in terms of metabolic stability and in terms of A_1, A_2 receptor binding and specificity Adenosine agonists with high selectivity for the A_1 or A_2 receptor are of potential interest as antiarrhythmics, anticonvulsants, antihypertensives and as other therapeutic agents. Several recent reports of highly active and selective nucleoside systems for both A_1 and A_2 receptors have focused attention on 2- and/ or N^6-modified adenosines [11-21] This paper reports on the synthesis and A_1, A_2 receptor binding activities of novel N^6-cyclosubstituted isoguanosine analogs and related C-2 functionalized compounds.

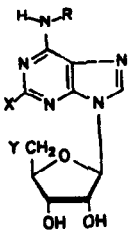
Results and Discussion

The synthetic design for the target compounds incorporated a series of N^6-monocyclic, bicyclic and tricyclic substitutions and a variety of C-2 functionalizations, both modifications of the parent adenosine molecule to increase receptor affinity and selectivity through hydrophobic, H-bonding and other interactions In addition, in some cases, 5'-modification was also carried out The 19 novel compounds synthesized are shown in Table 1

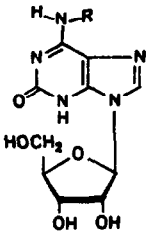
N^6-Substituted adenosine analogues (compounds **1** and **2**) were prepared by treatment of 6-chloropurine ribonucleoside with the appropriate amine in the presence of triethylamine in refluxing chloroform or chloroform/ ethanol Syntheses of compounds incorporating a 2-iodo modification along with an N^6-cyclosubstitution (**3-8**), a 2-iodo modification along with an N^6-cyclosubstitution and a 5'-chloro modification (**9,10**), or a 2-chloro modification along with the N^6-cyclomodification (**11-12**) were carried out as shown in Scheme I A thermally-induced radical deamination-halogenation reaction[22,23] was used to synthesize the key intermediates 6-chloro-2-iodo-9-(2',3',5'-tri-O-acetyl-β-D-ribofuranosyl)purine (**21**) and 2,6-dichloro-9-(2',3',5'-tri-O-acetyl-β-D-ribofuranosyl)purine (**23**) from the 2-amino-6-chloro precursor **20** The 6-chloro group was selectively displaced with the appropriate amine in the presence of triethylamine and subsequently deprotected using either NH_3/ C_2H_5OH or $NaOCH_3$/ CH_3OH to provide the target molecules **3-8** or **11-12** It should be mentioned that the halogen at the 2-position has been found to be quite resistant to displacement under the reaction conditions used The 5'-chloro modified compounds **9** and **10** were prepared from precursors **4** and **5** by forming the 2',3'-O-isopropylidene derivatives, transforming the 5'-hydroxyl group to the 5'-chloro group using N-chlorosuccinimide and triphenylphosphine in THF to give **26**,[24] and then deprotecting with 1M HCl at 60 °C for 1-2 h

The synthetic pathway for the preparation of the N^6-cyclosubstituted-2-oxo-1,2-dihydroadenosines (**13** - **19**) is shown in Scheme II Compounds **13** and **19** were prepared via a thermally-induced radical deamination-

Table 1. Structures of 2-Unsubstituted, 2-Halogenated, and 2-Hydroxy N^6-Cyclosubstituted Adenosine Analogues

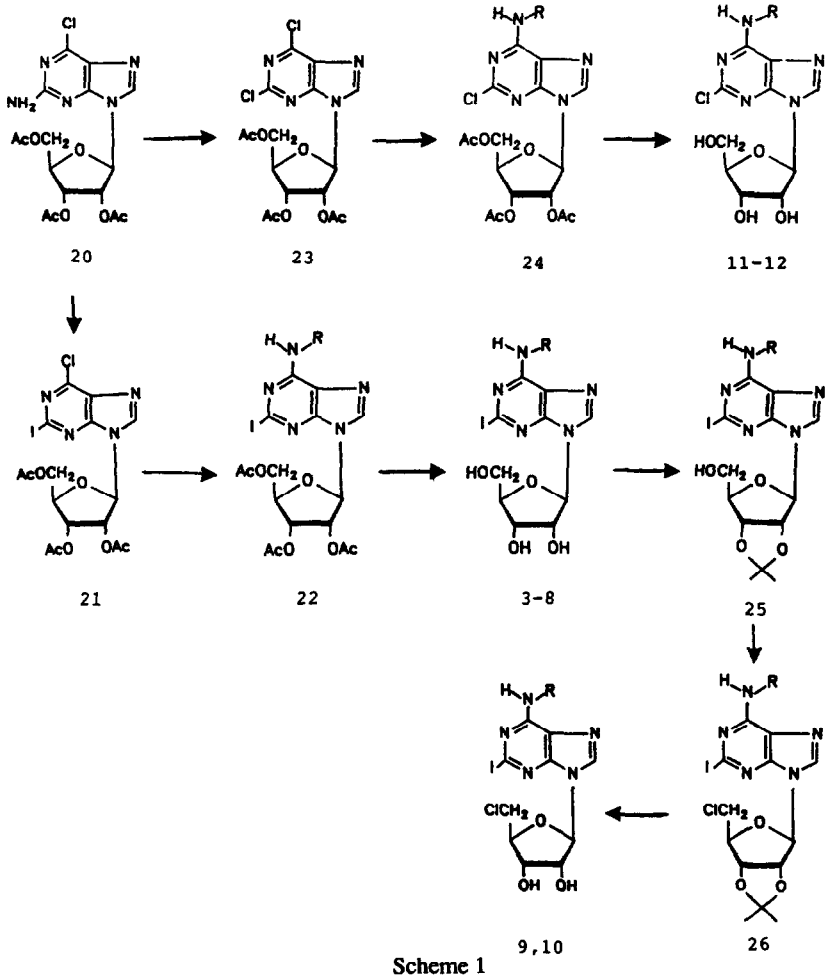


1 - 12



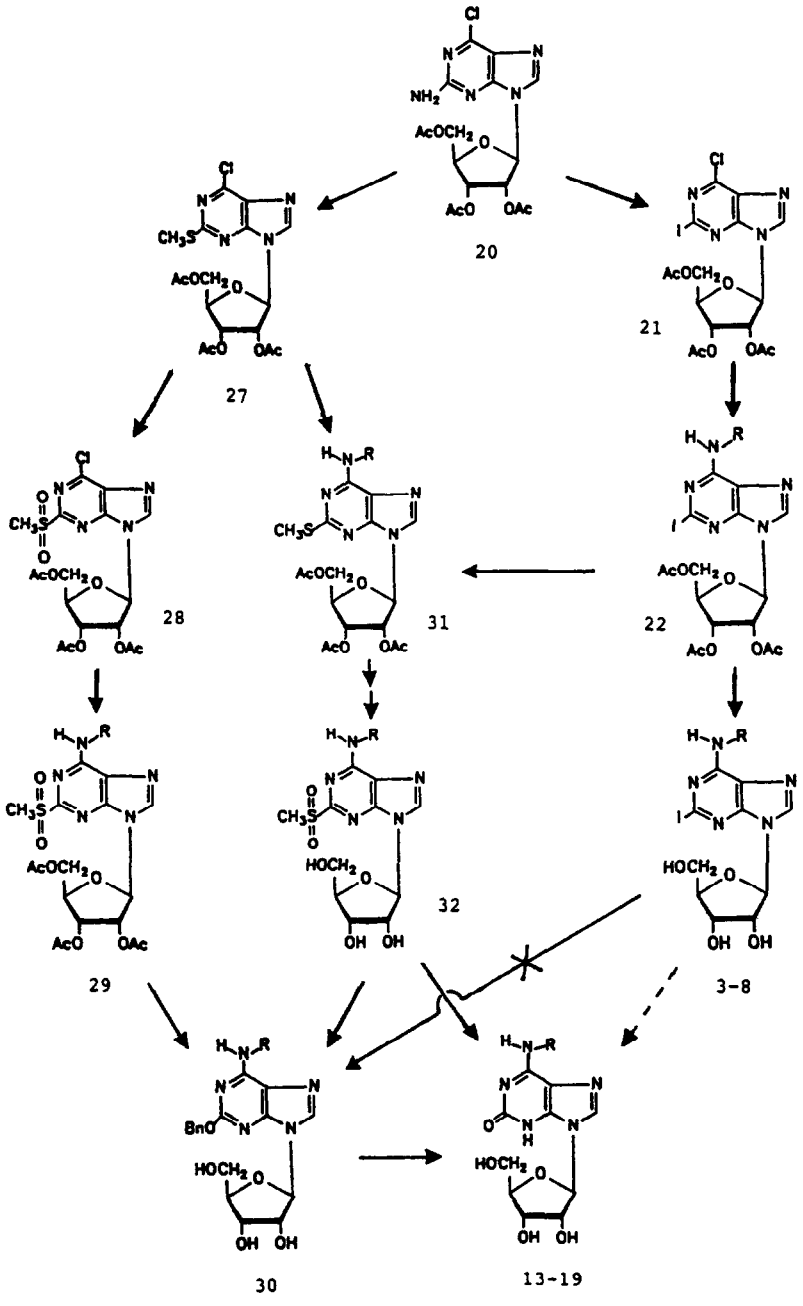
13 - 19

Compound	R	X	Y	mp, °C	Formula
1	3-noradamantyl	H	OH	89-92	$C_{19}H_{25}N_5O_4$
2	1-pyrrolidinyl	H	OH	108-110	$C_{14}N_{20}N_6O_4$
3	cyclopropyl	I	OH	119-121	$C_{13}H_{16}IN_5O_4$
4	cyclobutyl	I	OH	109-112	$C_{14}H_{18}IN_5O_4$
5	cyclopentyl	I	OH	173-175	$C_{15}H_{20}IN_5O_4$
6	cyclohexyl	I	OH	110-115 dec.	$C_{16}H_{22}IN_5O_4$
7	cycloheptyl	I	OH	115-118	$C_{17}H_{24}IN_5O_4$
8	endo-2-norbornyl	I	OH	128-130	$C_{17}H_{22}IN_5O_4$
9	cyclobutyl	I	Cl	140-143	$C_{14}H_{17}ClIN_5O_3$
10	cyclopentyl	I	Cl	78-80	$C_{15}H_{19}ClIN_5O_3$
11	cyclopropyl	Cl	OH	113-116	$C_{13}H_{16}ClN_5O_4$
12	3-noradamantyl	Cl	OH	120-123	$C_{19}H_{24}ClN_5O_4$
13	cyclopropyl			158-161	$C_{15}H_{17}N_5O_5$
14	cyclobutyl			167-170	$C_{14}H_{19}N_5O_5$
15	cyclopentyl			186-188	$C_{15}H_{21}N_5O_5$
16	cyclohexyl			170-172	$C_{16}H_{23}N_5O_5$
17	cycloheptyl			155-157	$C_{17}H_{25}N_5O_5$
18	2-decahydronaphthyl			175-180 dec.	$C_{20}H_{29}N_5O_5$
19	endo-2-norbornyl			179-186 dec.	$C_{17}H_{23}N_5O_5$



Scheme 1

thioalkylation which converted the 2-amino-6-chloropurine nucleoside **20** to the corresponding 2-methylthio compound **27**.[25] Oxidation of the sulfide group in **27** to the sulfone functionality with $KMnO_4$ in HOAc[16] facilitated subsequent selective displacement of the 6-chloro group from **28** with the appropriate amine to give the N^6-cyclosubstituted sulfone **29** Introduction of the lactam functionality was achieved by displacement of the 2-methylsulfonyl group thermally with benzyloxide anion and subsequent cleavage of the benzyl group in **30** utilizing a hydrogenolysis reaction to give compounds **13** and **19** Compounds **14, 17,** and **18** were prepared by displacing the 6-chloro group of **27** with the appropriate amine in the presence of triethylamine to provide compounds **31.** The latter were deprotected with $NaOCH_3$/ CH_3OH and oxidized with oxone (potassium peroxymonosulfate)[25] to yield the methylsulfonyl compounds **32** The methylsulfonyl group in **32** was then



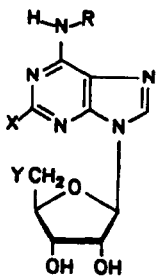
Scheme II

displaced with the benzyloxy anion to give **30** from which **14, 17** and **18** were prepared as described above The 2-methylsulfonyl group in **32** can be directly converted to the 2-oxo functionality by heating **32** at 70 °C in 1M NaOH to provide 40 % of the desired target molecules (**13 - 19**) along with degradation products

The isoguanosine agonists **15** and **16** were prepared from the appropriate 2-iodo-N^6-cyclosubstituted purine ribonucleoside **22** by utilizing a photochemically-induced dehalogenation-thioalkylation reaction[26] to form the 2-methylthio-N^6-cyclosubstituted analogues **31**. Subsequent reactions to reach the target compounds **15** and **16** were the same as those described above Interestingly, attempts to prepare the N^6-substituted-2-oxo analogues directly from the 2-iodo-N^6-substituted compounds **3-8** utilizing a photochemically-induced hydration reaction[27] produced only low yields of the desired product. In contrast, the same reaction with 2-iodoadenosine (i e the compound without N^6-cyclosubstitution) gave natural isoguanosine in 55 % purified yield [27] Finally, attempts to displace the 2-iodo group from compounds **3-8** with benzyloxide anion resulted in only low yields of the corresponding 2-benzyloxy compounds Thus, the synthetic pathways utilizing the sulfone intermediates described above were the best approaches to the isoguanosine compounds

The affinities of the isoguanosine analogues and related compounds in A_1, A_2 receptor binding are summarized in Table 2 Binding data for adenosine, N^6-cyclopentyladenosine and isoguanosine are included to provide a basis for comparison The data in Table 2 are relative to values obtained in these assays for two commonly used standards, N^6-cyclohexyladenosine for the A_1 receptor (6 nM) and 5'-N-ethylcarboxamido-adenosine for the A_2 receptor (17 nM) It is clear from the data that a number of the N^6-cyclosubstituted isoguanosines show excellent A_1 agonist activity There appears to be a trend in terms of correlation of ring size with receptor binding for the monocyclosubstituted compounds with the highest selectivity being obtained for the five- and six-membered ring compounds (**15, 16**) Decreases in specificity occur on either side of this N^6-ring size with greater loss in selectivity for the seven- membered ring compound (see **14** and **17**) The decalin system **18** (data not included in Table 2), showed poor A_1 agonist activity and poor A_1 selectivity However, the endo-norbornyl compound, **19**, showed excellent A_1 receptor binding (35 nm) and high A_2/A_1 selectivity (2,286) Its receptor binding selectivity is comparable to that of another one of our compounds, 2-iodo-N^6-cyclopentyladenosine, **5** Our results suggest that there may be specific binding involving both the 2- and 6-positions of the adenosine system involving the A_1 receptor Hydrophobic groups at the N^6 position, particularly those with five- or six-membered mono or bicyclic rings, appear to interact and be accomodated into the proposed S1, S2 and S3 subregions[28] within the A_1 receptor Certain electronegative groups capable of hydrogen bonding at the 2-position (e g Cl, I, O) may contribute to enhanced binding to the A_1 receptor and/ or a decreased affinity for the A_2 receptor Alternatively, the absence of large hydrophobic groups on nitrogen

Table 2. Affinities of the More Active Isoguanosine Analogues and Related Compounds in A_1, A_2 Receptor Binding Assays



COMPOUNDS	X	R	Y	K_i (nM) A_1	A_2	A_2/A_1
Adenosine	H	H	OH	12.8	37	2.9 [29]
N^6-Cyclopentyl-adenosine	H		OH	0.6	462	783 [30]
Isoguanosine	OH	H	OH	94	331	3.5 [29]
1	H		OH	30	8,500	283
2	H		OH	8	2,800	350
5	I		OH	20	40,000	2,000
10	I		Cl	180	17,000	94
12	Cl		OH	67	23,000	343
14	OH		OH	55	15,000	273
15	OH		OH	19	7,500	395
16	OH		OH	40	15,000	375
17	OH		OH	70	6,000	86
19	OH		OH	35	80,000	2,286

or oxygen at the 2-position (e g 2-phenylamino, 2-phenethoxy) contribute to decreasing A_2 receptor affinity Other synthetic studies to further delineate the structural requirements for the hydrogen bonding recognition site and the hydrophobic pocket in terms of biological activity are currently in progress

Experimental Section

Melting points are uncorrected and were determined on a Thomas-Hoover melting point apparatus fitted with a microscope Preparative layer chromatography plates were prepared by coating six 20 cm x 20 cm plates with a slurry made from 150 g of E. Merck PF_{254} silica gel in 400 mL of water The silica gel plates were allowed to dry slowly and were then activated for 3 h at 150 °C Flash chromatography was carried out in glass columns packed with 230-400 mesh silica gel Nuclear magnetic resonance spectra were recorded on JEOL Model FX90Q and on Bruker Model AC300 pulse Fourier transform NMR spectrometers Ultraviolet spectra were recorded on a Varian Cary Model 219 or a Gilford Response spectrophotometer Infrared spectra were recorded on a Mattson Cygnus 25 Fourier transform instrument Elemental analyses were carried out by Galbraith Laboratories, Inc , Knoxville, TN

General Method for the Preparation of Compounds 1 and 2. 6-(3-Noradamantylamino)-9-(β-D-ribofuranosyl)purine (1). A solution of 6-chloro-9-(2',3',5'-tri-O-acetyl-β-D-ribofuranosyl)purine (0 30g, 0 88 mmol), 3-aminonoradamantane (0 43g, 3 2 mmol), and Et_3N (0 32 g, 3 2 mmol) in $CHCl_3$ (20 mL) was refluxed under N_2 for 48 h The solvent was evaporated under reduced pressure and the residue was dissolved in absolute ethanol (50 mL) and the flask was charged with anhydrous NH_3 at 0 °C and left standing at room temperature for 24 h. The solvent was evaporated under reduced pressure and the residue was purified chromatographically using silica gel plates with 10 % MeOH/$CHCl_3$ as eluant The product was crystallized from EtOH/Et_2O to provide 0 21 g (60% overall yield) of the title compound **1** mp 89-92 °C, ^{1}H-NMR (Me_2SO-d_6) δ 0 85-2 23 (m, 13H), 3.58 (m, 2H), 3 98 (m, 1H), 4 16 (m, 1H), 4 59 (m, 1H), 5 31 (br m, 3H), 5 84 (d, 1H), 7 51 (s, 1H), 8 20 (s, 1H), 8.33 (s, 1H), UV (EtOH) 274 nm (ε 15,944)

Anal Calcd for $C_{19}H_{25}N_5O_4$ C, 58 90, H, 6 50, N, 18 08 Found C, 58 28, H, 6 51, N, 18 62

6-(1-Pyrrolidinyl)-9-(β-D-ribofuranosyl)purine(2). The compound was prepared as described for **1** but with pyrrolidine as base It was purified on silica gel and crystallized from EtOH/Et_2O (15% yield). mp 108-110 °C, ^{1}H-NMR (Me_2SO-d_6) δ 1 75-2 95 (m, 8H), 3 60 (m, 2H), 3 98 (m, 1H), 4 13 (m, 1H), 4 60 (m, 1H), 5 10-5 42 (m, 3H), 5 90 (d, 1H), 8 20 (s, 1H), 8 35 (s, 1H), 8 76 (s, 1H), UV (EtOH) 271 nm (ε 15,934)

Anal Calcd for $C_{14}H_{20}N_6O_4$. C, 49 99, H, 5 99, N, 24 99 Found C, 49 54, H, 5 67, N, 24 63

General Method for the Preparation of Compounds 3-8. 6-Cyclopentylamino-2-iodo-9-(β-D-ribofuranosyl)purine (5). A solution of 6-chloro-2-iodo-9-(2',3',5'-tri-O-acetyl-β-D-ribofuranosyl)purine **21** (0 22g, 0 4 mmol), cyclopentylamine (0 04 g, 0.5 mmol), and Et_3N (0 5 g, 0 5 mmol) in refluxing chloroform (40 mL) was stirred for 2 h. The solvent was evaporated and the residue was dissolved in absolute ethanol (30 mL), and the solution was saturated with anhydrous ammonia at 0 °C The solution was allowed to stand at room temperature for 24 h The solvent was then removed under reduced pressure and the residue triturated with o-xylene and the acetamide/o-xylene azeotrope and excess o-xylene were removed by distillation and the residue purified by thin-layer chromatography eluting with 10 % methanol/chloroform to provide 0.15 g (82 % combined yield) of **5** mp 173-175 °C, ^{1}H NMR (Me_2SO-d_6) δ 1 61 (m, 9H), 3 63 (m, 2H), 3 93 (m, 1H), 4 13 (m, 1H), 4 52 (m, 1H), 5 01 (m, 1H), 5 21 (m, 1H), 5 43 (m, 1H), 5 79 (d, 1H), 8 15 (m, 1H), 8 28 (s, 1H), UV (EtOH) 274 5 nm (ε 14,980)

Anal Calcd. for $C_{15}H_{20}IN_5O_4$. C, 39 06; H, 4 37, N, 15.18. Found. C, 39.12, H, 4.42, N, 14 60

6-Cyclopropylamino-2-iodo-9-(β-D-ribofuranosyl)purine (3). Prepared from **21** in 84% combined yield, after crystallization from EtOH/Et_2O/hexanes: mp 119-121 °C, ^{1}H-NMR (Me_2SO-d_6) δ 0 67-0 76 (m, 4H), 3 09 (m, 1H), 3 58 (m, 2H), 3 92 (m, 1H), 4 11 (m, 1H), 4 49 (m, 1H), 4 98 (m, 1H), 5 15 (d, 1H), 5 41 (d, 1H), 8 29 (m, 2H), UV (EtOH) 273 nm (ε 15,135).

Anal Calcd for $C_{13}H_{16}IN_5O_4$ C, 36 04, H 3 72, N, 16 17. Found C, 35 76; H, 3 78, N, 15 79

6-Cyclobutylamino-2-iodo-9-(β-D-ribofuranosyl)purine (4) Prepared from **21** in 81% combined yield after crystallization from EtOH/Et_2O/hexanes m.p 109-112 °C dec., ^{1}H-NMR (Me_2SO-d_6) δ 1 65-2 20 (m, 7H), 3 61 (m, 2H), 3 96 (m, 1H), 4.09 (m, 1H), 4 52 (m, 1H), 5 00 (t, 1H), 5 17 (m, 1H), 5.44 (d, 1H), 5 83 (d, 1H), 8 33 (s, 1H), 8.47 (d, 1H), UV (EtOH) 274 nm (ε 15,080).

Anal Calcd. for $C_{14}H_{18}IN_5O_4$· C, 37 60, H 4.06, N, 15 66. Found C, 36.91, H, 4 53; N, 14 75

6-Cyclohexylamino-2-iodo-9-(β-D-ribofuranosyl)purine (6). Prepared from **21** in 58% combined yield after crystallization from EtOH/Et_2O/hexanes. m p 110-115 °C dec , ^{1}H-NMR (Me_2SO-d_6) δ 1 23-1 75 (m, 11H), 3 64 (m, 2H), 3 95 (m, 1H), 4 13 (m, 1H), 4 50 (m, 1H), 5 02 (m, 1H), 5.19 (m, 1H), 5 46 (m, 1H), 5 80 (d, 1H), 8 03 (d, 1H), 8 28 (s, 1H), UV (EtOH) 273 5 nm (ε 14,480)

Anal. Calcd for $C_{16}H_{22}IN_5O_4$. C, 40 43, H, 4.66, N, 14 73. Found C, 40 69 H, 4 87, N, 14 64.

6-Cycloheptylamino-2-iodo-9-(β-D-ribofuranosyl)purine (7). Displacement of the 6-chloro group of the key intermediate, **21**, followed by deprotection and crystallization from EtOH/Et_2O/hexanes provided **7** in 82 %

combined yield· m.p. 115-118 °C; ^{1}H-NMR (Me_2SO-d_6) δ 1.55 (m, 13H), 3.61 (m, 2H), 3 95 (m, 1H), 4 15 (m, 1H), 4 53 (m, 1H), 5.00 (m, 1H), 5.17 (m, 1H), 5 41 (m, 1H), 5 83 (d, 1H), 8 07 (d, 1H), 8 32 (s, 1H); UV (EtOH) 273.5 nm (ε 16,070)

Anal Calcd. for $C_{17}H_{24}IN_5O_4$: C, 41 73; H, 4 94, N, 14 31. Found· C, 42.32; H, 5.21, N, 13 90.

2-Iodo-(endo-2-norbornylamino)-9-(β-D-ribofuranosyl)purine (8). The amine displacement of **21** with endo-2-norbornylamine, deprotection, chromatographic purification on silica gel and crystallization from EtOH/Et_2O/hexanes provided **8** in 81 % yield· mp 128-130 °C, ^{1}H-NMR (Me_2SO-d_6) δ 1.24-2 16 (m, 11H), 3 60 (m, 2H), 3 94 (m, 1H), 4 14 (m, 1H), 4 52 (m, 1H), 4 99 (m, 1H), 5 18 (m, 1H), 5.42 (m, 1H), 5.82 (d, 1H), 8 16 (d, 1H), 8 29 (s, 1H), UV (EtOH) 274 nm (ε 16,643).

Anal Calcd for $C_{17}H_{22}IN_5O_4$· C, 41.84, H, 4 54, N, 14 35. Found. C, 42.17, H, 4 75; N, 13 78.

General Method for the Preparation of Compounds 9,10. 6-Cyclopentylamino-2-iodo-9-(5'-chloro-5'-deoxy-β-D-ribofuranosyl)purine (10). A solution of **5** (2 97g, 6 4 mmol), tosic acid monohydrate (1 22g, 6 4 mmol) and 2,2-dimethoxypropane (12 0 g, 116 mmol) in acetone (80 mL) was stirred at room temperature for 16 h The reaction was quenched with aqueous $NaHCO_3$ The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography using silica gel with 2% MeOH/$CHCl_3$ as the eluant to provide 1 69 g (53 %) of 6-cyclopentylamino-2-iodo-9-(2',3'-O-isopropylidene-β-D-ribofuranosyl)purine **25** as a white foam: ^{1}H-NMR (Me_2SO-d_6) 1 33 (s, 3H), 1 54 (s, 3H), 1 60 (m, 9H), 3 53 (d, 2H), 3 70 (m, 1H), 4 19 (m, 1H), 4 93 (dd, 1H), 5.26 (dd, 1H), 6 05 (d, 1H), 8.21 (d, 1H), 8 37 (s, 1H); UV (EtOH) 273 nm A solution of this isopropylidene protected nucleoside (1 53 g, 3 1 mmol) and triphenylphosphine (1 61 g, 6.1 mmol) in THF (30 mL) was stirred at 0 °C as N-chlorosuccinimide (0 82g, 6 1 mmol) in THF (10 mL) was added dropwise The reaction mixture was stirred at room temperature with exclusion of moisture for 16 h at which time MeOH was added to quench The solvent was evaporated under reduced pressure, the residue dissolved in MeOH, and 1N HCl was added The reaction mixture was stirred at 50-60 °C for 2 h, the pH adjusted to neutrality with NaOH, and the solvent removed The residue was purified by flash chromatography on silica gel eluting with 2 % MeOH/$CHCl_3$, then by thin-layer chromatography using silica gel plates eluting with 10 % MeOH/$CHCl_3$ and subsequently crystallized from EtOH/Et_2O/ hexanes to provide 0 96g (66 % combined yield) of **10** mp 78-80 °C, ^{1}H-NMR (Me_2SO-d_6) δ 1 62-1 93 (m, 9H), 3 91 (m, 2H), 4 17 (m, 2H), 4 67 (m, 1H), 5 52 (m, 2H), 5 86 (d, 1H), 8 17 (d, 1H), 8 27 (s, 1H), UV (EtOH) 273 nm (ε 15,330)

Anal Calcd. for $C_{15}H_{19}ClIN_5O_3$· C, 37 56; H, 4 00, N, 14 60 Found C, 37 64, H, 4 17; N, 14.26.

6-Cyclobutylamino-2-iodo-9-(5'-deoxy-5'-chloro-β-D-ribofuranosyl)purine (9). The combined yield for the 5'-modification of **4** to provide **9** was 40 % mp 140-143 °C; ^{1}H-NMR (Me_2SO-d_6) δ 1 64-2 19 (m, 7H), 3 91 (d, 2H), 4 16 (m, 2H), 4.65 (m, 1H), 5 52 (m, 2H), 5.85 (d, 1H), 8 28 (s, 1H), 8 46 (d, 1H); UV (EtOH) 274 nm (ε 16,864).

Anal Calcd. for $C_{14}H_{17}ClIN_5O_3$· C, 36.11, H, 3 68, N, 15.04 Found C, 36 15; H, 3 77; N, 14 54

General Method for the Preparation of Compounds 11,12. 2-Chloro-6-(3-noradamantylamino)-9-(β-D-ribofuranosyl)purine (12) A solution of **23** (0 31 g, 0 70 mmol), 3-amino- noradamantane (0 38g, 2 8mmol) and Et_3N (0 28 g, 2 8 mmol) in $CHCl_3$ (20 mL) was stirred at 60 °C for 16 h with exclusion of moisture The solvent was evaporated under reduced pressure and the residue was dissolved in absolute EtOH (40 mL) and the flask charged with anhydrous ammonia at 0 °C The reaction was left to stand at room temperature for 24 h The residue was purified by flash chromatography on silica gel using 2 % MeOH/$CHCl_3$ as eluant. The residue was further purified on silica gel plates eluting with 10 % MeOH/$CHCl_3$ and crystallized from EtOH/Et_2O/hexanes to provide 0 20 g (66 % combined yield) of **12**: mp 120-123 °C, ^{1}H-NMR (Me_2SO-d_6) δ 1 20-2 64 (m, 13H), 3 59 (m, 2H), 3 96 (m, 1H), 4 14 (m, 1H), 4 51 (m, 1H), 5.03-5 43 (m, 3H), 5.81 (d, 1H), 8 18 (s, 1H), 8 36 (s, 1H), UV (EtOH) 274 nm (ε 16,734)

Anal Calcd for $C_{19}H_{24}ClN_5O_4$ C, 54 09, H, 5 73, N, 16 60 Found C, 54 05; H, 5 69; N, 16 70

6-Cyclopropylamino-2-chloro-9-(β-D-ribofuranosyl)purine (11). The compound was prepared from **23** and crystallized from EtOH/ Et_2O/hexanes (85 % combined yield) mp 113-116 °C; ^{1}H-NMR (Me_2SO-d_6) δ 0 66-0 77 (m, 4H), 3 03 (m, 1H), 3 58 (m, 2H), 3 92 (m, 1H), 4 10 (m, 1H), 4 48 (m, 1H), 5 01 (m, 1H), 5 13 (m, 1H), 5 42 (m, 1H), 5 83 (d, 1H), 8 37 (m, 2H), UV (EtOH) 273 nm (ε 16,866)

Anal Calcd for $C_{13}H_{16}ClN_5O_4$ C, 45.69, H, 4 72, N, 20 49 Found C, 45 02; H, 4 83, N, 20 02

General Method for the Preparation of Compounds 13, 14, 17-19. 6-Cyclopropylamino-1,2-dihydro-2-oxo-9-(β-D-ribofuranosyl) purine (13). A solution of **20** (4 8g, 11 4 mmol), dimethyl disulfide (0.74g, 114 mmol) and n-pentyl nitrite (2 4g, 22 8 mmol) in CH_3CN (50 mL) was stirred under nitrogen at 60 °C for 16 h The solvent and excess CH_3SSCH_3 were evaporated under reduced pressure The residue was incorporated into a silica plug and purified by flash chromatography using silica gel and 1 % MeOH/$CHCl_3$ as eluant to provide 3 8g (73 %) of **27** ^{1}H-NMR (Me_2SO-d_6) δ 1 97 (s, 3H), 2 08 (s, 3H), 2 12 (s, 3H), 2 64 (s, 3H), 4 40 (m, 3H), 5 71 (m, 1H), 6 06 (m, 1H), 6 32 (d, 1H), 8.71 (s, 1H), UV (EtOH) 264, 304 5 nm The latter compound (4 2g, 9 2 mmol) was oxidized with aqueous $KMnO_4$ (4 4g, 27 6 mmol) in glacial acetic acid (30 mL) at 0 °C for 3 h

Water (100 mL) and $CHCl_3$ (100 mL) were added and mixture was stirred at room temperature. The $CHCl_3$ layer was washed twice with 5 % $NaHCO_3$, once with brine solution, and dried over Na_2SO_4. The product was purified by flash chromatography on silica gel eluting with 2 % MeOH/$CHCl_3$ to provide 3.5g (75 %) of **28**. The sulfone methyl singlet of **28** appears at 3.34 ppm The IR shows absorbance due to the sulfone moiety at 1306 and 1130 cm^{-1} The N^6-cyclopropyl group was introduced by reacting **28** (3 1g, 6.3 mmol) with cyclopropylamine (2 2g, 38 mmol), and Et_3N (1 3g, 12.7 mmol) in $CHCl_3$/EtOH at room temperature for 2 h The solvent was evaporated and the residue was purified by flash chromatography on silica gel eluting with 1 % MeOH/$CHCl_3$ to provide **29** in 59 % yield ^{1}H-NMR (Me_2SO-d_6) 0 71-0.91 (m, 4H), 2 09 (s, 3H), 2.10 (s, 3H), 2 16 (s, 3H), 3 15 (m, 1H), 3.36 (s, 3H), 4 42 (m, 3H), 5 61 (m, 1H), 5 82 (m, 1H), 6.24 (d, 1H), 6 30 (m, 1H), 8 06 (s, 1H), UV (EtOH) 268 nm, IR 1306, 1130 cm^{-1} (sulfone) A solution of **29** (1 9g, 3 7 mmol) and sodium benzyloxide (0 85g, 3.7 mmol in 7 0 mL of benzyl alcohol) in DMF (10 mL) was stirred at 50 °C for 1 5 h Ammonium chloride (8 0g) was then added and stirring was continued at room temperature for 1 h The DMF was evaporated off under reduced pressure and the residue was incorporated into a silica plug and purified by flash chromatography eluting initially with $CHCl_3$ to remove excess benzyl alcohol, then with 4 % MeOH/$CHCl_3$ to elute the product, 2-benzyloxy-6-cyclopropylamino-9-(β-D-ribofuranosyl)purine **30** as an oil in 75 % yield A solution of **30** (1 2g, 2 9 mmol) and 10 % Pd/C (0 4g) in EtOH (100 mL) was hydrogenated at 44 psi of H_2 for 16 h to effect hydrogenolysis of the benzyloxy group to introduce the 2-oxo functionality The Pd/C was filtered off and the solvent was evaporated under reduced pressure. The residue was purified on silica gel plates eluting initially with $CHCl_3$, then 15 % MeOH/$CHCl_3$ and then crystallized from EtOH/Et_2O to provide 0.54g (60 %) of (**13**): mp 158-161 °C; ^{1}H-NMR (Me_2SO-d_6) δ 0 61-0 77 (m, 4H), 2 93 (m, 1H), 3 57 (m, 2H), 3 90 (m, 1H), 4.09 (m, 1H), 4 51 (m, 1H), 4.80-5 53 (m, 3H), 5 65 (d, 1H), 7.67 (m, 1H), 7 89 (s, 1H), UV (EtOH) 249 (ε 8703), 302 nm (10,230), IR (carbonyl) 1629cm^{-1}.

Anal. Calcd. for $C_{13}H_{17}N_5O_5$ H_2O. C, 45.75, H, 5 61, N, 20.52 Found: C, 45 92, H, 5 36, N, 20 08

6-Cyclobutylamino-1,2-dihydro-2-oxo-9-(β-D-ribofuranosyl)purine (14). This compound was prepared from **27** and crystallized from isopropanol/Et_2O (17 % overall yield) m p 167-170 °C; ^{1}H-NMR (Me_2SO-d_6) δ 1 72-2.17 (m, 7H), 3 59 (m, 2H), 3 93 (m, 1H), 4.08 (m, 1H), 4 48 (m, 1H), 4 74 (m, 1H), 5 08 (m, 1H), 5 32 (m, 1H), 5.70 (d, 1H), 7.98 (s, 1H), 8.15 (m, 1H), UV (EtOH) 249 (ε 9,110), 284 5 (8,260), 302 5 nm (6,890), IR (carbonyl) 1652 cm^{-1}

Anal. Calcd for $C_{14}H_{19}N_5O_5$· C, 49 85, H, 5.68, N, 20 76. Found C, 49 22, H, 5 70, N, 20 06

Cycloheptylamino-1,2-dihydro-2-oxo-9-(β-D-ribofuranosyl)purine (17). Prepared from **27** in 17%

overall yield after crystallization from isopropanol/Et_2O· m.p. 155-157 °C; ^{1}H-NMR (Me_2SO-d_6) δ 1.56 (m, 13H), 3 61 (m, 2H), 3 96 (m, 1H), 4 11 (m, 1H), 4 49 (m, 1H), 5.05-5.39 (m, 3H), 5.70 (d, 1H), 7.71 (m, 1H), 7 99 (s, 1H), UV (EtOH) 248.5 (ε 10,000), 284 (8,830), 302 nm (8,170); IR (carbonyl) 1636 cm^{-1} Anal Calcd for $C_{17}H_{25}N_5O_5 H_2O$ C, 51 38, H, 6 34; N, 17 62. Found· C, 51 69, H, 6.92; N, 17 34.

6-(2-Decahydronaphthylamino)-1,2-dihydro-2-oxo-9-(β-D-ribofuranosyl)purine (18). Prepared from **27** and crystallized from isopropanol/Et_2O (8% overall yield). m p 175-180 °C dec., ^{1}H-NMR (Me_2SO-d_6) δ 1 54 (m, 17H), 3 59 (m, 2H), 3 96 (m, 1H), 4.11 (m, 1H), 4.50 (m, 1H), 5 07-5 35 (m, 3H), 5.69 (d, 1H), 7 64 (m, 1H), 7 97 (s, 1H), UV (EtOH) 249 (ε 9,490), 283.5 (8,920), 302 nm (7,250), IR (carbonyl) 1636 cm^{-1}. Anal Calcd for $C_{20}H_{29}N_5O_5$: C, 57.27, H, 6 97, N, 16 69. Found C, 57 79, H, 7.12, N, 16 39

6-(endo-2-Norbornylamino)-1,2-dihydro-2-oxo-9-(β-D-ribofuranosyl)purine (19) Prepared from **27** and crystallized from isopropanol/Et_2O (22% overall yield). mp 179-186 °C dec , ^{1}H-NMR (Me_2SO-d_6) δ 1 38-2 17 (m, 11H), 3 58 (m, 2H), 3 92 (m, 1H), 4 09 (m, 1H), 4 50 (t, 1H), 4 96-5.48 (m, 3H), 5 68 (d, 1H), 7 96 (m, 2H), UV (EtOH) 249 (ε 11,542), 284 (10,635), 302 nm (9579), IR (carbonyl) 1634 cm^{-1}. Anal Calcd for $C_{17}H_{23}N_5O_5 H_2O$ C, 51 64, H, 6 37, N, 17 71 Found· C, 51 21, H, 6 18; N, 17 34

General Method of Preparation for Compounds 15, 16. 6-Cyclopentylamino-1,2-dihydro-2-oxo-9-(β-D-ribofuranosyl)purine (15). A solution of 6-cyclopentylamino-2-iodo-9-(2',3',5'-tri-O-acetyl-β-D-ribofuranosyl)purine, **22**, (3 6 g, 6 2 mmol) and dimethyl disulfide (14 6 g, 155 mmol) in anhydrous acetonitrile (80 mL) was photolyzed in a Rayonet photochemical reactor (254 nm) for 40 h. Excess solvent and dimethyl disulfide were removed under reduced pressure The residue was incorporated into a silica plug and purified by flash chromatography eluting product with 1 1 EtOAc/hexanes to provide 1 9 g (60 %) of **31** ^{1}H-NMR (Me_2SO-d_6) δ 1 61 (m, 9H), 1 98 (s, 3H), 2 07 (s, 3H), 2 11 (s, 3H), 4 34 (m, 3H), 5 67 (m, 1H), 6 04-6 13 (m, 2H), 7 87 (m, 1H), 8 20 (s, 1H), UV (EtOH) 243, 280 nm A solution of deprotected **31** (2.6 g, 6 5 mmol) in methanol (50 mL) was cooled to 0 °C and a solution of oxone (6.0 g, 9 7 mmol) in acetate buffer (pH 4 2, 200 mL) was added dropwise The reaction mixture was allowed to attain room temperature and was stirred for 4 h and then neutralized with NaOH The solvent was removed and the residue triturated with 9 1 $CHCl_3$/ MeOH and filtered The filtrate was incorporated into a silica gel plug and purified by flash chromatography eluting 1.6 g (56 %) of **32** The sulfone methyl singlet appears at 3 32 ppm and the UV shifts to 269 nm The IR shows absorbance due to the sulfone group at 1304 and 1132 cm^{-1} A solution of the latter compound 1 3 g, 3 3 mmol) in DMF (30 mL) was stirred at 60 °C for 2 h with sodium benzyloxide (0 45 g, 19 6 mmol in excess

benzyl alcohol). The reaction was cooled to room temperature and ammonium chloride (2.1 g) was added and stirring continued for an additional hour. The DMF was removed under reduced pressure (50 °C) and the resulting syrup was incorporated into a silica plug and purified by flash chromatography eluting initially with $CHCl_3$ to remove excess benzyl alcohol and then with 6 % CH_3OH/ $CHCl_3$ to elute 6-cyclopentylamino-2-benzyloxy-9-(β-D-ribofuranosyl)purine 0.7 g (50 %)· mp 96-100 °C dec ; ^{1}H-NMR (Me_2SO-d_6) δ 1 60 (m, 9H), 3 62 (m, 2H), 3 91 (m, 1H), 4.12 (m, 1H), 4 62 (m, 1H), 5 13 (m, 3H), 5 33 (s, 2H), 5.80 (d, 1H), 7.38 (m, 5H), 7 67 (d, 1H), 8 14 (s, 1H); UV (EtOH) 274 nm. A solution of the latter compound (0 4 g, 1 mmol) and 10 % Pd/C (0 1 g) in EtOH (50 mL) was hydrogenated at 30 psi of H_2 for 14 h to effect hydrogenolysis of the benzyloxy group to introduce the 2-oxo functionality The Pd/C was removed by filtration and the solvent was evaporated under reduced pressure. The residue was purified on silica gel plates (15 % MeOH/ $CHCl_3$ and subsequently crystallized from isopropanol/Et_2O to provide **15**. mp 186-188 °C, ^{1}H-NMR (Me_2SO-d_6) δ 1 59-1 81 (m, 9H), 3.58 (m, 2H), 3 94 (m, 1H), 4.09 (m, 1H), 4 49 (m, 1H), 5.09-5 53 (m, 3H), 5 67 (d, 1H), 7.71 (m, 1H), 7.97 (s, 1H), UV (EtOH) 248.5 (ε 9,410), 284 (8,210), 302 5 (7,860), IR (carbonyl) 1639 cm^{-1}
Anal Calcd for $C_{15}H_{21}N_5O_5 H_2O$. C, 48 78, H, 5 73; N, 18.96 Found C, 48.44; H, 6 17, N, 18 56.

6-Cyclohexylamino-1,2-dihydro-2-oxo-9-(β-D-ribofuranosyl)purine (16). Prepared from **22** and crystallized from isopropanol/ Et_2O (15% overall yield) m.p 170-172 °C, ^{1}H NMR (Me_2SO-d_6) δ 1 32-1 88 (m, 11H), 3 60 (m, 2H), 3.95 (m, 1H), 4 10 (m, 1H), 4 49 (m, 1H), 5 12-5 38 (m, 3H), 5 69 (d, 1H), 7.64 (m, 1H), 7 97 (m, 1H); UV (EtOH) 248 5 (ε 9,290), 284 5 (7,770), 302 5 nm (7,990), IR (carbonyl) 1643 cm^{-1}
Anal Calcd. for $C_{16}H_{23}N_5O_5$ $0.5H_2O$ C, 51 33, H, 6 46, N, 18 70. Found C, 50 92; H, 6 61, N, 18 34.

A_1, A_2 Affinity Studies

A_1 Affinity studies were carried out in adenosine deaminase (ADA) pre-treated rat brain membranes in Tris-HCl buffer (pH 7.4) using [^{3}H]-N^6-cyclohexyladenosine (specific activity 20 Ci/mmol) using previously described procedures [29] A_2 Receptor binding was measured in ADA-pretreated rat striatal membranes in Tris-HCl buffer using [^{3}H]-5'-N-ethylcarboxamidoadenosine ([^{3}H]-NECA, specific activity 23 Ci/mmol) Cyclopentyladenosine was used to eliminate the A_1 component. These studies were performed at Gensia Pharmaceuticals The procedure has been described [29]

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